

**UNITED STATES DEPARTMENT OF COMMERCE****United States Patent and Trademark Office**

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

M ✓

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/181,311	10/28/98	LEE	A APV-382.01

025181
FOLEY, HOAG & ELIOT, LLP
PATENT GROUP
ONE POST OFFICE SQUARE
BOSTON MA 02109

HM12/0509

EXAMINER

TURNER, S

ART UNIT	PAPER NUMBER
----------	--------------

1647

15

DATE MAILED: 05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.

09/181,311

Applicant(s)

Lee et al

Examiner

Sharon L. Turner, Ph.D.

Art Unit

1647



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2-20-01
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above, claim(s) 1-6 and 10-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-9 and 31-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) ☐ Other: _____

Art Unit: 1647

Response to Amendment

1. The amendment filed 2-20-01 has been entered into the record and has been fully considered.
2. Claims 1-33 are pending.
3. Claims 1-6 and 10-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.
4. Applicants have traversed the withdraw of amended claims 12-21 on the grounds that the restriction requirement was not based on the functional activity of the genes identified. This is not found persuasive because the claims as amended are comprised of different steps, reagents and functions. In addition, the functional activity of the genes identified appear to be patentably distinct for the purpose of identifying agents. Thus, the methods are distinct each from the other, are separable and constitute a search burden to the examiner.

The requirement is still deemed proper and is therefore made FINAL.

5. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Rejections Maintained

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Art Unit: 1647

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 7-9 stand rejected under 35 U.S.C. 101 as set forth in Paper No. 11, mailed 8-16-00 because the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility.

Claims 7-9 also stand rejected under 35 U.S.C. 112, first paragraph as set forth in Paper No. 11, mailed 8-16-00. Specifically, since the claimed invention is not supported by either a specific and substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that genes identified as being up- or down regulated during differentiation or migration of smooth muscle cells are specifically useful as diagnostic markers of numerous diseases as specified at pp. 1-2 and p. 45, lines 9-23. Alternatively applicants submit that the markers can be used to determine the stage of differentiation of the cell or the likelihood of developing a disease associated with dedifferentiation of smooth muscle, which utilities are substantial and provide a real world context. Applicants further submit that the method has a well established utility since a person of ordinary skill in the art would appreciate the invention as useful, specific, substantial and credible.

Applicants arguments filed 2-20-01 have been fully considered but are not persuasive because the claimed invention does not provide an identified gene which is up or down regulated, diagnostically correlated or useful to determine disease incidence, likelihood or cell

Art Unit: 1647

differentiation state. Applicants claims are directed to a generally recognized research method for which alone there is no specific and substantial utility or well established utility. While the method has potential for use as a general research tool which *may* ultimately result in the development of specific and substantial utilities for identified genes, the discovery process itself does not provide the public with the immediate beneficial knowledge as required to make, practice or perform any specific or substantial product or process within the context of a real world use. Applicants are directed to MPEP 2107 and the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

9. Claim 7 stands rejected under 35 U.S.C. 102(b) as set forth in Paper No. 11, mailed 8-16-00 as being anticipated by Shah et al., Cell 85:331-343, May 3, 1996.

Applicants argue that Shah fails to disclose immortalized neural crest cells as the cells are naturally occurring precursors as disclosed at p. 341.

Art Unit: 1647

Applicants arguments filed 2-20-01 have been fully considered but are not persuasive because the naturally occurring precursors are inherently immortalized as they undergo symmetrical, self-renewing divisions in culture for at least 5-6 days in vitro (i.e., are capable of serial propagation). There is no defining characteristic of an immortalized cell which is absent from the cells of Shah. Thus, the reference teachings anticipate the claimed invention.

10. Claim 7 stands rejected under 35 U.S.C. 102(e) as set forth in Paper No. 11, mailed 8-16-00 as being anticipated by Anderson et al., US Patent 5,672,499 filed June 7, 1995 and issued September 30, 1997.

Applicants arguments to the above rejection filed 2-20-01 have been jointly presented with respect to '654 rejection as follows. As applicant has chosen to address the references jointly the arguments and rebuttal are presented below.

11. Claim 7 stands rejected under 35 U.S.C. 102(e) as set forth in Paper No. 11, mailed 8-16-00 as being anticipated by Anderson et al., US Patent 6,001,654 filed April 25, 1997 and issued Dec. 14, 1999.

Applicants argue that the references fail to teach differentiation of immortalized neural crest cells into smooth muscle cells. Applicants further submit that although the references contain an example of immortalized neural crest stem cells that the references fail to provide evidence that the procedures result in immortalization and that the references further fail to teach conditions for differentiation of immortalized neural crest cells to smooth muscle cells, in particular for 'uniformly' differentiating neural crest cells into smooth muscle cells as amended

Art Unit: 1647

in the claims. Applicants reference Example 15 of the '654 patent for comparison to the specification at p. 11, lines 18-28.

Applicants arguments filed 2-20-01 have been fully considered but are not persuasive. As acknowledged by applicants, the '654 and '499 references teach immortalized neural stem cells. The references further disclose for example that the immortalized cells survive selection in G418 and are characterized as disclosed for example at column 2, lines 10-25 of the '654 patent. However, in contrast to applicants assertion it is not a requirement that the references prove the cells are immortalized, they are presumed so. Applicants claims do not distinguish those characteristics of immortalization which distinguish applicants cells from the cells of the '499 or '654 patent as required. A prima facie case has been made as previously disclosed the cells of the cited references are clonal, proliferative as survive in culture for over 3 days, thus being immortalized. As to the references asserted deficiency in teaching conditions suitable for smooth muscle cell differentiation, it is noted that the conditions are disclosed for example in example 12 including incubation with TGF- β superfamily members such as BMP-2 and BMP-4. As to applicants new claim limitation, it is noted that the limitation is not considered to be patentably distinct. The specification does not teach the extent of uniformly differentiated cells which in comparison to those of the prior art distinguish over the prior art. The reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

Art Unit: 1647

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 7-9 stand rejected under 35 U.S.C. 103(a) as set forth in Paper No. 11, mailed 8-16-00 as being unpatentable over Shah et al., Cell 85:331-343, May 3, 1996, Anderson et al., US Patent 5,672,499, Anderson et al., US Patent 6,001,654, Baetscher et al., US Patent 5,922,601 and Liang et al., US Patent 5,599,672.

Applicants argue that neither the Shah et al., nor the Anderson et al., references teach or suggest immortalized neural crest cells which differentiate almost uniformly into smooth muscle cells and that neither Baetscher nor Liang cure this defect.

Applicants arguments filed 2-20-01 have been fully considered but are not persuasive. There is no element claimed which is different from the cited references. The cells are

Art Unit: 1647

immortalized as they are capable of clonal expansion and the cell differentiate uniformly into smooth muscle cells as noted by the references. Thus, the reference teachings render the claimed invention obvious.

New Rejections Based on Amendment

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 7-9 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants arguments with respect to the prior art of record appear to suggest a definition of "immortalized" not recognized by the examiner. The cells of the prior art record are capable in particular of clonal expansion in culture for 3-5 days and are thus considered to be thus immortalized. Applicants have failed to provide a limiting definition of that which constitutes an immortalized cell and thus the term appears to be indefinite in the art and specification as applicants appear to imply for example that an immortalized cell is required to be one which is transformed with an oncogene. Thus, applicants arguments appear to render the term indefinite as used in the claims.

16. Claims 7-9 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the

Art Unit: 1647

elements. See MPEP § 2172.01. The omitted elements are: the culture conditions which are sufficient for the neural crest cells to differentiate uniformly into smooth muscle.

The terms “culture conditions” “sufficient” and “differentiate uniformly” in claims 7-9, and 31-33 are relative terms which render the claims indefinite. The terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

17. Claim 7, 31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Darland et al., Developmental Biology, 176:62-75, May 25, 1996.

Darland et al., teach immortalized neural crest cells via transformation with the v-myc oncogene. The cells are induced to differentiate by culture conditions sufficient to provide the differentiation of smooth muscle cells as exemplified by the expression of smooth muscle actin. The smooth muscle actin is a gene identified as being up-regulated as identified by immunoreactivity which inherently indicates up-regulation of the RNA. The cells of Darland are not referred to as Monc-1 cells, however the cells are referred to as v-myc transformed neural crest stem cells and are thus deemed to be an equivalent, or inherently the same as Monc-1 cells as defined by the specification at p. 11, lines 29-34. Thus, the reference teachings anticipate the claimed invention.

18. Claims 7-9 and 31-33 are rejected under 35 U.S.C. 103 as being unpatentable over Dorland et al., Shah et al., Anderson et al., Liang et al., Baetscher et al., further in view of

Art Unit: 1647

Fauquet et al., PNAS 87(4):1546-50, Feb., 1990 and applicants specification as set forth at p. 12, lines 1-10.

Dorland et al., Shah et al., and Anderson et al., are as set forth above and in Paper No. 11, mailed 8-16-00 and teach identification of up- or down-regulated genes in neural crest stem cells induced to differentiate to smooth muscle cells via culture.

Liang et al., and Baetscher et al., are as set forth above and in Paper No. 11, mailed 8-16-00 and teach the analysis and cloning of genes in differentiating cells via analysis of mRNA via differential display.

However, the references do not teach such analysis in neural crest cells which include c-myc oncogene.

Fauquet et al., teach that c-myc, like v-myc transformed cells (as specified in Dorland) are immortalized. In addition, the specification at p. 12, lines 1-10 disclose that such transformation is recognized in the art as a substantially equivalent method of immortalizing cells for the purposes of prolonged cell culture and experimentation therein. Thus, in view of the teachings and knowledge of the skilled artisan it would have been prima facie obvious to the skilled artisan to analyze gene expression in c-myc transformed cells undergoing differentiation. One of skill in the art would be motivated to do such knowing that c-myc transformed cells are suitable equivalents for such purpose, the methodology of Liang and Baetscher and the teachings of Shah, Dorland and Anderson to discover differentially regulated gene targets for the purpose of further research and identification of differentially expressed genes during differentiation.

Art Unit: 1647

Status of Claims

19. No claims are allowed.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

21. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Art Unit: 1647

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.

May 3, 2001

**CHRISTINE J. SAOUD
PRIMARY EXAMINER**

Christine J. Saoud